EXHIBIT C

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DISEASE-MODIFYING DRUGS
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COMBINATION THERAPY IN RHEUMATOID ARTHRITIS: UPDATED SYSTEMATIC REVIEW

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SUMMARY

In a second update of a systematic review, many new developments in the combined drug treatment of rheumatoid arthritis (RA) are highlighted. In early RA patients, step-down bridge therapy that includes corticosteroids leads to much enhanced efficacy at acceptable or low toxicity. The effects on joint damage may be persistent, but the symptomatic effects are probably dependent on continued corticosteroid dosing. In late patients, cyclosporin improves a suboptimal clinical response to methotrexate, and the triple combination of methotrexate, sulphasalazine and hydroxychloroquine appears to be clinically better than the components. Other combinations are either untested, tested at low sample size, or show negative interaction. In view of the low volume of evidence, most studies need confirmation by replication.

KEY WORDS: Rheumatoid arthritis, Combined treatment, DMARDs, Glucocorticoids, Systematic review.

THERE is a trend among rheumatologists to treat rheumatoid arthritis (RA) patients earlier and more aggressively. New scientific evidence supports early intervention with disease-modifying anti-rheumatic drug (DMARD) therapy [1]. Rapid and adequate control of disease activity is aimed at the prevention of structural joint damage and subsequent loss of function and quality of life. In this setting, combining so-called DMARDs might lead to additive effects. Alternatively, doses might be reduced, and perhaps some of the toxicity avoided. Many rheumatologists already prescribe combination therapy, although until recently scientific evidence to support this policy was lacking. Over the last few years, an increasing number of high-quality trials have been published. We present a second update of a systematic review of combination therapy in RA [2, 3].

In combining DMARDs, three main strategies can be distinguished. In this review, the label 'step-up strategy' is reserved for trials in which patients with insufficient clinical benefit from one second-line agent continued the use of this first drug and had another (or placebo) added to this. The label 'parallel' was assigned to trials in which the patients started with a combination of new drugs, and 'step-down' to trials with sequential withdrawal of simultaneously started drugs, prescribed by protocol.

METHODS

Study identification

The MEDLINE database was searched from August 1992 (the closing date of the previous review) to July 1997 using the MeSH headings: 'arthritis, rheumatoid'; and 'drug therapy, combination'. The bibliographies of all retrieved articles were scrutinized for additional studies. The first authors of studies published only in abstract form were contacted. Such studies were eligible for inclusion if a full manuscript was available. Titles and abstracts (when available) were screened by one author (MB up to August 1992, ACV subsequently) and any article in English, French, German or Dutch that appeared potentially relevant was retrieved.

Study selection and validity assessment

First, the quality of the studies, and thus the strength of evidence, was scored on a three-point scale on the basis of two primary criteria: randomization and blinding. Accordingly, strong evidence came from randomized, double-blind studies; moderately strong evidence from studies that were randomized, but open or partially blinded; and weak evidence from all other studies. This score specified the maximum strength we felt a study could yield. A second set of criteria, modified from Sackett *et al.* [4] was then applied. These were: (a) adequate outcome assessment (blind and comprising toxicity); (b) adequate description of study patients (report of at least age and sex, some record on the previous disease severity and concurrent medication); (c) adequate description of the therapeutic manoeuvre (i.e. minimal potential of bias, with blinding, contamination, co-intervention and compliance properly addressed); (d) complete accounting of study patients in the results. To obtain the final quality score, points were subtracted for each of these criteria not met.

Data extraction and analysis

The results of the trials yielding moderately strong or strong evidence in the previous reviews (original and update) were added to the information from the new search. Data extracted from the selected studies

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included baseline patient characteristics, study and concomitant treatment, outcome measures, and details on toxicity, withdrawals and eligibility criteria for disease activity.

Clinical efficacy, i.e. improvement in clinical outcome measures, was compared between the combined-treatment group and the single-treatment group. In the case of more than one control group, comparisons were made between the combined-treatment group and each control group, but eventually the comparison with the best performing control group was decisive. The WHO/ILAR core set measures assessed efficacy [5]. These measures comprise tender and swollen joint count (or a score), pain assessment, patient and physician (or observer) global assessment, physical function index [here, in every case Health Assessment Questionnaire (HAQ) or a modification thereof], and acute-phase reaction [i.e. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]. When less than four of these measures had been assessed, first grip strength and second morning stiffness were selected as well. Four levels of efficacy were distinguished based on differences in improvement in the selected measures:

- combined treatment 'substantially more effective' ('++' in the summary table): significantly greater improvement in the combined-treatment group in at least half of the selected measures (minimum two out of four), plus improvement of at least 150% that of the control group;
- combined treatment 'more effective' ('+'): significantly greater improvement in at least half of the selected measures;
- 'positive trend' ('+?'): significantly greater improvement in at least 25% of the measures, or significantly greater improvement only in a predefined summary index of measures;
- 'no difference' ('='): the remainder.

When the total number of core set measures (plus grip strength and morning stiffness) was less than four, only trends were scored.

Toxicity was rated as increased ('+') when significantly more patients from the combined-treatment group were withdrawn from the study medication because of adverse events. Likewise, it was rated as decreased ('−') when significantly less patients from the combined-treatment group were withdrawn from the study medication because of adverse events. A significant difference (or trend) in numbers of adverse events not leading to withdrawal was rated as 'trend of more toxicity' ('+?') or 'trend of less toxicity' ('−?'). Where possible, results of statistical tests comparing the effect or toxicity of the different treatments were calculated or recalculated using the reported data.

RESULTS

Previous work had yielded eight relevant studies [2, 3]. Six of these eight provided 'strong' or 'moderately strong evidence' and are included in the final selection [6, 12, 14, 20, 24, 26]. The current search, covering the interval between August 1992 and July 1997, yielded 231 new citations. Together with previous reviews, this brings the total to 611 titles scanned, 100 were retrieved and 18 selected for review. Of the screened abstracts and titles, 38 were linked to a possibly relevant article. Three articles in Japanese [27–29] were not rated. Not selected articles were case reports, editorials, observational or non-randomized studies. Three studies that described adjuvant treatment with oral corticosteroids, androgens and oestrogens, respectively, were not included because they failed to meet the criterion of a one-type single DMARD control group [30–32]. Two studies described an extended follow-up or radiological assessments of an already selected article [33, 34]; the data from these publications were added to those of the original study [19, 20]. Two articles were found in the reference list of selected articles [9, 10]. Four possibly relevant reports in abstract form were found in abstract book supplements. The corresponding manuscripts of two recently published articles were obtained [21, 22].

The total of 29 (six old, 14 new) included trials are listed in Table I. The total number of patients included in these trials is 1952. All trials used a more or less strict criterion to verify the presence of active disease. The studies are ranked according to treatment strategy as well as the DMARDs of choice. Six studies describe a step-up strategy; two of these used cyclosporin, three used i.m. gold as anchor drug, and two methotrexate. Ten studies describe a parallel strategy; of these, six used methotrexate (all but one as anchor drug), six studies used antimalarials (one as anchor drug), three used sulphasalazine, one i.m. gold, dapsone or D-penicillamine (as anchor drugs); also used were aurano-fin and azathioprine (as additional drug; total more than 10, due to combinations). The studies with a step-down strategy (four in total) all used steroids [i.m. methylprednisone pulses or predniso(lo)ne orally]. Steroids were added to i.m. gold (in two studies) or sulphasalazine (also in two studies; in one study prednisolone was added together with methotrexate).

Studies with step-up strategy

Smyth *et al.* [6] added 75 mg/day cyclophosphamide or placebo to a stable and continued pre-trial dose of prednisone varying between 3 and 15 mg/day in 29 patients with established disease. After 6 months, outcomes in the combined-treatment group were significantly more improved in grip strength and an inflammatory index comprising swelling, redness, pain on motion, heat and tenderness, but not in ESR. Only one case of alopecia was reported in the combined-treatment group with no withdrawal due to toxicity in either group. Given the paucity of outcomes, this suggests a trend of increased efficacy with no increase in toxicity, but the disease activity at baseline was less in the placebo group.

Moreland *et al.* [7] performed a dose-finding study of monoclonal anti-CD4 antibody cM-T412 in three different doses or placebo added to stable treatment with methotrexate (≤ 15 mg week) in 64 patients with

TABLE I
Reviewed trials clustered by drug combination and combination strategy

First author	Ref.	Publication year	n patients	n groups	Compared drugs or combinations	Therapy strategy	Strength of evidence	Disease duration (yr)	Assessments at (month)	'O' score	Efficacy	Toxicity
Smyth	[6]	1975	29	2	(Pred CyP) *vs* Pred	Step-up	Moderate	>2	6	2/3	+	=
Mordhnd	[7]	1995	64	4	(MTX αCD4) *vs* MTX	Step-up	Strong	9	3	0/6	=	=
Tugwell	[8]	1995	148	2	(MTX CyA) *vs* MTX	Step-up	Strong	10	6	6/7	+ +	=
Bendix	[9]	1996	40	2	(AU CyA) *vs* AU	Step-up	Strong	11	6	1/7*	=	+ ?
Yasuda	[10]	1994	24	2	(AU Buc) *vs* AU	Step-up	Strong	8	3	3/4	+	+ ?
Porter	[11]	1993	142	2	(AU Hcq) *vs* AU	Step-up	Moderate	6	6	0/4	=	=
Scott	[12]	1988	101	2	(AU Hcq) *vs* AU	Parallel	Strong	2	12	1/4†	+ ?	+ ?
Faarvang	[13]	1993	91	3	(SSZ Hcq) *vs* SSZ *vs* Hcq	Parallel	Strong	7	6	0;2/5	=	=
Gibson	[14]	1987	72	3	(Dpen Cq) *vs* Dpen *vs* Cq	Parallel	Moderate	2	12	0;1/5	=	=
Haar	[15]	1993	80	3	(Daps Hcq) *vs* Daps *vs* Hcq	Parallel	Strong	2	6	1;1/4	=	=
Trnavsky	[16]	1993	40	2	(Hcq MTX) *vs* Hcq	Parallel	Strong	>2	6	2/5	+ ?	+ ?
Ferraz	[17]	1994	82	2	(MTX Cq) *vs* MTX	Parallel	Strong	8	6	2/4	+	+ ?
O'Dell	[18]	1996	102	3	(MTX SSZ‡ Hcq)‖ *vs* (SSZ‡ Hcq) *vs* MTX	Parallel	Strong	9	9	2;2/5	+ ?	=
Williams	[19]	1992	335	3	(MTX AUR) *vs* MTX *vs* AUR	Parallel	Strong	5	12	0;0/5	=	+ ?
Willkens	[20]	1992	209	3	(MTX AZA) *vs* MTX *vs* AZA	Parallel	Strong	8	12	0;2/6	=	+ ?
Haagsma	[21]	1997	105	3	(MTX SSZ) *vs* MTX *vs* SSZ	Parallel	Strong	<1	6	0;0/7	=	=
Boers	[22]	1997	155	2	(SSZ MTX Predl) *vs* SSZ	Step-down	Strong	<1	6	6/7	+ +	−
van Gestel	[23]	1995	40	2	(AU Pred) *vs* AU	Step-down	Strong	2	3	3/6	+ +	=
Corkill	[24]	1990	59	2	(AU MP) *vs* AU	Step-down	Strong	6	3	3/4	+ +	+ ?
Ciconelli	[25]	1996	38	2	(SSZ MP§) *vs* SSZ	Step-down	Moderate	6	6	0/4	=	=

'O' score is the number of clinical WHO/ILAR core set outcome measures (see Methods) significantly better in the combined-treatment group in comparison with control group(s). Results from comparisons with two control groups are separated by a semicolon (;). Behind the slash (/) is the total number of assessed core set measures. NB. The efficacy rating is derived from the O score, and in some cases also from improvement in two non-core set measures (grip strength and morning stiffness) or from improvement in a predefined primary outcome index.

AU, i.m. gold salts; AUR, auranofin; AZA, azathoprine; Buc, bucillamine; αCD4, monoclonal anti-CD4 antibodies (three doses); Cq, chloroquine; CyA,cyclosporin; CyP, cyclophosphamide; Daps, dapsone; Dpen, D-penicillamine; Hcq, hydroxychloroquine; MP, methylprednisone pulses; MTX, methotrexate; Pred, prednisone; Predl, prednisolone; SSZ, sulphasalazine.

*Non-core set measures of patient's and (non-blind) clinician's assessment of overall efficacy did show significantly more improvement in the combined-treatment group.

†The combined-treatment group showed significantly better scores for a validated disease activity index based on five variables in a flow chart.

‡Low sulphasalazine doses in the combined treatment groups: 1 g/day.

§Low methylprednisone doses: 3 mg/kg/pulse.

refractory RA. Assessments after 3 months treatment and 4 i.v. pulses of anti-CD4 did not show any relevant between-group difference in clinical efficacy or toxicity.

Tugwell *et al.* [8] added cyclosporin or placebo to methotrexate in 148 patients with established disease and insufficient response to methotrexate alone. After 6 months, all outcomes with the exception of ESR were substantially and significantly better in the combined-treatment group (HAQ and global assessments $P < 0.001$). Expressed in percentages, improvement as compared with placebo varied between 19 and 26%. The frequency of adverse effects was similar to prior trials of methotrexate and cyclosporin used alone. A threshold of 30% increase in serum creatinine for dose reduction resulted in a relatively low mean cyclosporin dose (3 mg/kg). Eighty per cent of the included patients had stable co-medication with low-dose corticosteroids ($\leq$10 mg).

Bendix and Bjelle [9] added cyclosporin or placebo to i.m. gold treatment in 40 patients. After 6 months the combined treatment showed increased efficacy only in patient's global assessments of overall health and clinical efficacy, and non-blind assessments by a treating physician ($P < 0.01$ and <0.05); other core set measures, including blinded observer's global assessment, showed no difference. No serious adverse effects were noted. Higher blood pressure and signs of renal function impairment were found more often in the cyclosporin-treated group, also dose reduction was required significantly more often in the cyclosporin group. Adverse events requiring symptomatic treatment occurred only in eight patients; four in each treatment group. Six months after the end of combination therapy, all differences had disappeared.

Yasuda *et al.* [10] added bucillamine, a drug developed in Japan, or placebo to i.m. gold treatment in 24 patients. After 3 months, the combined-treatment group had significantly better outcomes in swollen joint count, physician's global assessment and CRP ($P < 0.05$), and similar outcomes (trend) in tender joint count and ESR. Withdrawal for lack of efficacy only occurred in the control group (five patients), and withdrawal due to toxicity occurred more often in the combined-treatment group (5 *vs* 3).

Porter *et al.* [11] added hydroxychloroquine or placebo to i.m. gold treatment in 142 patients. After 6 months, no differences were evident between the groups. Withdrawal (for all reasons) was comparable in both trial groups (~28%). Owing to the lack of description of previous medication and patient compliance, the strength of evidence was rated as moderate.

Studies with parallel strategy

Scott *et al.* [12] also tested the combination hydroxychloroquine and i.m. gold, but in a parallel strategy against i.m. gold alone in 101 patients. After 12 months of treatment, the combination showed a positive trend in all of the outcomes, but only CRP ($P = 0.01$) and the *a priori* defined composed summary index of disease activity were significantly better ($P < 0.05$). There was less progression of joint damage on radiographs in the combined-treatment group, although this did not reach significance. The total withdrawal rate was high: 42%. The authors report that toxicity might be enhanced as 18 patients in the combined-treatment group *vs* 10 in the control group were withdrawn for adverse effects.

Fiarvang *et al.* [13] compared the combination of sulphasalazine and hydroxychloroquine with each of these agents alone in 91 patients. Analysis of study completers after 6 months treatment showed no difference between combined treatment and single sulphasalazine treatment. However, combined treatment did show better outcomes in swollen joint count and patient's global assessment compared to hydroxychloroquine alone ($P < 0.05$). In our view, this only confirms that sulphasalazine is a more effective drug than hydroxychloroquine. Both groups showed similar progression of joint damage on radiographs. Withdrawal, for adverse effects as well as other reasons, in this trial was frequent in all treatment groups (32%).

Gibson *et al.* [14] compared the combination of D-penicillamine and chloroquine in comparison with each of these alone in 72 patients. After 12 months, the decreases in ESR in the combined-treatment group were significantly larger compared to chloroquine, but not compared to D-penicillamine. Improvements in morning stiffness, joint tenderness and swollen joint score and grip strength did not show significant contrasts between treatment groups. There were significantly more adverse effects in the combined-treatment and the D-penicillamine groups compared with chloroquine.

Haar *et al.* [15] compared the combination of hydroxychloroquine and dapsone with each of these drugs alone in 80 patients. After 6 months of treatment, the combination showed a positive trend with a significant difference only in one measure: ESR, but the baseline values for ESR were also better in this treatment group. Patients treated with combined dapsone and hydroxychloroquine showed less progression of joint damage, but this result was weakened by serious disbalance between groups in baseline values. Withdrawals for toxicity were more numerous in the combined-treatment group, but this difference was not significant (5 *vs* 3 and 4; $P = 0.11$).

Tsnavsky *et al.* [16] compared the combination of hydroxychloroquine and methotrexate with hydroxychloroquine and placebo in 40 patients. After 6 months, the combined treatment showed a positive trend with significantly better outcomes in two of five core set measures: patient's global assessment and ESR ($P < 0.05$). The combined-treatment group contained more patients without progression of joint damage, but the report allows no conclusion on whether this difference was significant. Withdrawal for adverse effects was rare (one case).

Farraz *et al.* [17] compared the combination of methotrexate and chloroquine to methotrexate alone in 32 patients. After 6 months, the combination was more effective in tender joint count ($P = 0.04$) and HAQ ($P = 0.04$). The authors state that combined treatment was slightly more toxic (and effective),

although only three patients were withdrawn due to adverse effects (two of whom had combined treatment). The percentage loss to follow-up (partially related to non-compliance) was quite high (39%) in this study.

O'Dell *et al.* [18] compared the combination of methotrexate, sulphasalazine and hydroxychloroquine to the combination of sulphasalazine and hydroxychloroquine, and to methotrexate alone, in 102 patients. The dose of sulphasalazine (1 g/day) was low. Every 3 months, dose adjustments of methotrexate were allowed, guided by assessments of the effect of therapy. The main assessment of efficacy was after 9 months when no further opportunity was offered to adjust the methotrexate dose in case of insufficient therapy response (by definition <50% improvement in modified Paulus criteria). At this time, 27/31, 23/35 and 28/36 patients were considered responders (χ^2 test: triple therapy *vs* sulphasalazine–hydroxychloroquine $P = 0.04$; *vs* methotrexate $P = 0.32$; overall $P = 0.12$). Based on survival analyses, the authors report significantly more patients with a response to triple therapy after 9 months and conclude that triple therapy results in enhanced efficacy with no increase in toxicity. Non-responders were considered therapy failures and further report on follow-up was restricted to responders. At 9 months of follow-up and according to the rules of this review, triple therapy only showed a positive trend: significantly better swollen and tender joint counts compared to methotrexate, and significantly better swollen joint count and ESR compared to hydroxychloroquine–sulphasalazine. At 2 yr follow-up (with 38% patients still in follow-up), the between-treatment group contrasts were larger (and highly significant), but this concerns only the patients who had a sufficient response according to the modified Paulus criteria at month 9. Withdrawal for toxicity was rare at year 2, but data on withdrawals due to adverse events at month 9 were not available; however, overall withdrawal at month 9 was about equal.

Williams *et al.* [19] compared the combination of methotrexate and oral gold ($n = 106$) against treatment with each of these agents alone in 335 patients. After 48 weeks, none of the five assessed core set measures showed more benefit in the combined-treatment group. Withdrawals for toxicity occurred somewhat more frequently in the combined-treatment group (21% *vs* 15% and 14%; trend, not significant). Subsequently, Lopez-Mendez *et al.* [33] reported no differences between the groups in progression of radiographic scores at week 48.

Willkens *et al.* [20] compared the combination of methotrexate and azathioprine with each of these drugs alone in 209 patients. Data on ESR and HAQ were subsequently added in a letter [35], and data on 48 weeks of follow-up and radiological progression were published later [34]. The combination was not better in the between-group comparisons (withdrawals considered as treatment failures), except for ESR when combined treatment was compared to single azathioprine ($P = 0.03$). The authors also report a trend of less radiographic progression in the methotrexate group. Adverse effects occurred primarily in the combined-treatment and azathioprine group (trend). Numbers of withdrawn patients per treatment group due to toxicity are not available, but therapeutic interventions related to adverse events were reported more often in the combined treatment group (48% *vs* 25% and 21%).

Haagsma *et al.* [21] compared the combination of methotrexate and sulphasalazine with each of these drugs alone in 105 patients. After 52 weeks, the combination was not more effective in any of the four core set or other measures. Response to treatment was exceptionally good in all groups: 74% met the preliminary ACR criteria for improvement [36]. Fewer patients were withdrawn for toxicity reasons in the single methotrexate treatment group compared to the combined-treatment group ($P = 0.025$). In contrast with most other trials, the patients included in this study had early disease. These results agree with those of a trial only published in abstract form [37], but contrast with the results of an open trial (not included in this review) in which patients with insufficient reaction to sulphasalazine first stopped this drug and afterwards were randomized to combined methotrexate–sulphasalazine, or methotrexate alone. Here, the combined-treatment group showed significantly better outcomes [38].

Studies with step-down strategy

Boers *et al.* [22] compared the combination of sulphasalazine (2 g/day), methotrexate (7.5 mg/week) and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) with sulphasalazine alone in 155 patients. The last assessment of therapy effect of combined treatment was at week 28 of follow-up as prednisolone and methotrexate were tapered and stopped after 28 and 40 weeks, respectively. At week 28, significantly better outcomes in the combined-treatment group were seen in all composite measures and all but one of the core set measures ($P < 0.002$). In these measures, the improvement in the combined-treatment group was 2-fold or almost 2-fold that of the single sulphasalazine group. Seventy-two per cent of the patients in the combined-treatment group *vs* 49% in the sulphasalazine group had improved according to the ACR criteria ($P = 0.006$). The clinical difference between the groups decreased and was no longer significant after prednisolone was stopped, and there were no further changes after methotrexate was stopped. Withdrawal for toxicity during the first 28 weeks was significantly less in the combined-treatment group (1 *vs* 7; $P = 0.04$). The frequency of adverse events not resulting in withdrawal was similar in both groups. In addition to the clinical results, progression of joint damage in the combined-treatment group was one-third that in the sulphasalazine group. This effect persisted until week 80, i.e. 1 yr after the withdrawal of prednisolone which started at week 28 of follow-up.

Van Gestel *et al.* [23] compared the combination of i.m. gold (50 mg/week) and prednisone (initially

10 mg/day for 12 weeks, then tapered to zero in 2-weekly steps) with i.m. gold alone in 40 patients. The main assessment was at week 12, just before prednisone was gradually withdrawn. At this time, all five assessed core set measures showed significantly greater improvement in the combined-treatment group: the magnitude of this improvement is not reported. The improvement in a composite index, the disease activity score (DAS) [39], in the combined-treatment group was more than 2-fold that with single gold treatment. Progression of joint damage was similar in both groups. Withdrawal due to toxicity was the same in both groups after 20 weeks (four patients in each group). The authors report troublesome rebound effects in the combined-treatment group after withdrawal of prednisone. This appears to be based on a single significant between-group comparison in an array of 13: in week 20 of follow-up, the DAS in the combined-treatment group was worse than in the control group. However, at this moment (and up to week 44), patients in both groups were still better than at baseline. After 44 weeks (32 weeks after the beginning of tapering prednisone), no between-group difference remained.

Corkill *et al.* [24] compared the addition of three pulses of 120 mg i.m. methylprednisone (at week 0, 4 and 8) to i.m. gold in 59 patients. After 12 weeks, the combined treatment was significantly better in three of four core set measures: improvement in pain and physical function was more than twice as high, and joint count almost twice as high. After 24 weeks, the between-group difference had almost disappeared. Progression of joint damage was similar in both groups. Withdrawal due to toxicity during 24 weeks was more frequent in the combined-treatment group, but not significantly so.

Finally, Ciconelli *et al.* [25] compared the addition of three low-dose i.v. methylprednisone pulses (5 mg/kg), at baseline, month 1 and 2, with sulphasalazine alone in 38 patients. Eighty per cent of the patients in both groups had a prescription of oral corticosteroids. In the 6 month study period, no differences between treatment groups in efficacy or toxicity were found. The relatively low dose of methylprednisone in a population already treated with corticosteroids may have decreased the possible contrast. This important co-intervention with oral corticosteroids was the reason to rate the strength of evidence from this trial as moderate.

Figure 1 summarizes the heterogeneity of the findings of this systematic review graphically. Except for corticosteroids, there appears to be no trend for an overall beneficial effect of a particular drug in a combination. The figure also shows the lack of data: low sample size in most trials, and many untested combinations.

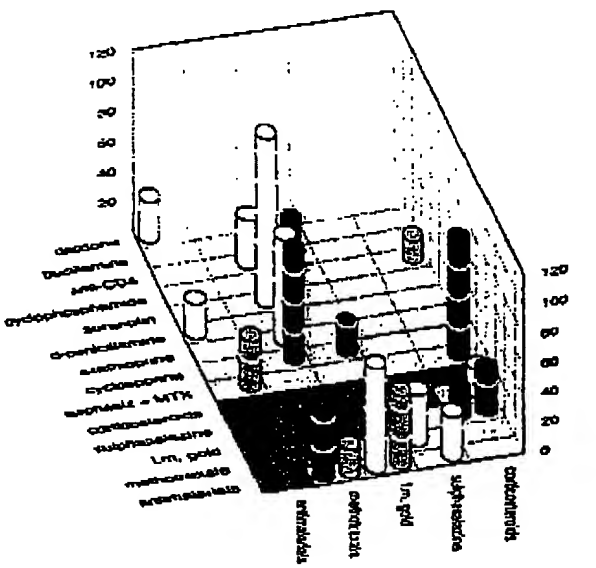

FIG. 1.—Three-dimensional summary of the efficacy of combination therapy. From the perspective of the five most frequently used drugs, the matrix describes the combinations of all single drugs reviewed, and one two-drug combination. Each bar describes a specific combination trial: its length reflects the sample size of the combined-treatment group, its shade reflects the evidence that combined treatment is better than the single drug(s). Dark grey, strong evidence that the combination is better or much better; light grey, moderate evidence that the combination is better (any evidence or trend); white, no evidence that the combination is better. Because the five primary drugs are repeated on the long axis, a dark area in the matrix indicates overlap.

DISCUSSION

In its second update since 1991, this review highlights exciting new developments in the combined drug treatment of RA. In early disease, step-down bridge therapy with corticosteroids appears safe and, in the right dose and duration, truly disease modifying; however, the effect on disease activity (not damage) appears to be dependent on continuation of low-dose corticosteroids. This strengthens Kirwan *et al.*'s [30] finding of the damage control resulting from corticosteroid adjuvant therapy, a study not included in this review because anti-rheumatic therapy was not uniformly applied in the control group. In late disease, patients with a suboptimal response to methotrexate improve clinically with cyclosporin, and some patients on triple therapy with methotrexate, sulphasalazine and hydroxychloroquine appear clinically better off than patients on a two-drug combination or methotrexate alone. This lifts the gloom from the other studies compiled so far, where negative interaction (i.e. results of the combination are the same or only slightly better than the single drugs) prevails, often at the cost of somewhat increased toxicity. Interestingly enough, rheumatologists have not waited for these first positive results or heeded the many negative trials; according to two recent surveys published in abstract [40, 41], they almost universally embrace combination therapy.

Felson *et al.* [42] recently published a meta-analysis on combination therapy in which he pooled the available data. He found a negative answer to the question:

'Does combination therapy on average make a difference compared to average single therapy?' In our view, the heterogeneity in combinations, strategies and patient material makes this a less interesting research question. As shown in Fig. 1, each combination needs careful study of its potential in several trials, which can subsequently be pooled.

Despite the results of Tugwell *et al.*'s study, we feel a step-down or parallel strategy in general shows more potential than a step-up strategy. The reason is that step-up trials select patients who have demonstrated less responsiveness to therapy, thus a priori decreasing the chance of future response. Also, if non-compliance is the basis for lack of efficacy, non-compliant patients are more prone to being selected in a trial with non-responders, and the subsequent therapy will again be more prone to fail.

Although methodology has improved significantly in recent years, we still found a number of problems. Most selected studies had small patient numbers, and notably in the studies with negative results, post hoc sample size calculations were often lacking. In theory, type II errors can be minimized by sufficiently large sample sizes. In practice, it is often hard to find eligible patients. Reliable and responsive measurements can also help to record an actual contrast between groups. For example, with joint score assessments, reliability can be improved by frequent training of the assessors.

Co-intervention and contamination are important issues in clinical trials and, obviously, any type of co-intervention should be reported in a transparent way. Co-intervention with low-dose corticosteroids was very common in many of the trials selected for this review. Steroids quickly reduce disease activity. With less room for improvement induced by the investigated treatment, demonstration of contrast between treatment groups becomes harder. Corticosteroids are generally known as symptom-relieving drugs. The data summarized here make it clear that systemic corticosteroids should be considered as disease-controlling anti-rheumatic therapy (DCART) [43]. Accordingly, uncontrolled co-intervention with corticosteroids in RA clinical trials needs reconsideration.

In conclusion, in early RA patients, step-down bridge therapy that includes corticosteroids leads to much enhanced efficacy at acceptable or low toxicity. The effects on joint damage may be persistent, but the symptomatic effects are probably dependent on continued corticosteroid dosing. In late patients, cyclosporin improves a suboptimal clinical response to methotrexate, and the triple combination of methotrexate, sulphasalazine, and hydroxychloroquine appears clinically better than the components. Other combinations are either untested, tested at low sample size, or show negative interaction. In view of the low volume of evidence, most studies need confirmation by replication.

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